Rheumatology Nurses Society
Patient Education Series

HANDLING THE
HARD QUESTIONS:

What Our Patients Are Asking Us About Immunology

The Purpose of this Document

Rheumatology healthcare professionals field dozens of questions each day from their patients about immunology, and they need to be able to properly and effectively communicate appropriate responses. This pocket guide includes a brief summary of evidence surrounding some of the most common—and challenging—questions today's patients are asking about their immune system. We hope you find this guide useful for your professional development and that it assists you with your day-to-day patient management.

CONTENTS

How does a normal immune system work?

A normal, healthy, functioning immune system is key to protecting against disease and foreign invaders. In order for the immune system to work properly, a number of complex interactions between different types of immune cells must occur in harmony. The complexity of the immune system can make it difficult for even seasoned providers to appreciate exactly how it all works. In a basic sense, it can be broken down into two types of immunity—innate and adaptive—which work together to respond to foreign invaders.[1]

The **innate immune system** is responsible for preventing foreign invaders from entering the body in the first place as well as the initial response to invaders when they do enter the body. Much of innate immunity is made up of physical barriers,

such as the body's epithelial layers; the mucus layers that protect the respiratory, gastrointestinal, and genitourinary tract; and the epithelial cilia.[2] The initial inflammatory release of complement and cytokines is also part of the innate immune response.

When a foreign invader is encountered in the body, the innate response is responsible for identifying the invader and mounting the initial, rapid, non-specific immune response. There are large numbers of cells in the innate immune system that are always circulating throughout the body, ready to mobilize and attack any invader. These cells include macrophages, which engulf as many of the invaders as they can.[1] It is the job of macrophages to present a piece of the foreign object, called an antigen, to the cells of the adaptive immune system.

The second set of responses to a foreign invader comes from the **adaptive immune system**, which launches an immune response to very specific targets that are able to evade or overcome the innate response.[3] These cells recognize specific pathogens, toxins, or allergens, but have fewer helpers circulating throughout the body. Since there are fewer of these cells available to encounter a foreign agent, they must quickly proliferate to provide the necessary numbers to mount an effective response. It can take up to a few days for antigen-specific T and B cells to proliferate and mount a response to a foreign invader. The majority of these cells will live for a short time.

Naïve B cells are capable of recognizing a foreign invader that is circulating through the body.[3] Once they do, B cells begin to divide rapidly and

differentiate so they can begin to make antibodies against the specific antigen, referred to as humoral immunity. This response is especially good at targeting extracellular microbes, including bacteria, extracellular phases of viruses, and some fungi.

T cells mount a cell-mediated immune response, which begins when a naïve T cell encounters a piece of the invader presented to it by an antigen presenting cell (APC).[3] T cells are especially good at protecting against intracellular microorganisms (bacteria, viruses, and parasites) and tumors, and are key in rejecting transplanted tissue. Helper T cells proliferate and help activate B cells, other T cells, and phagocytes. Cytotoxic T cells are responsible for killing infected cells that B cells mark with an antibody.

Once a foreign invader is removed from the body, most of the activated lymphocytes die off, ending the immune response and allowing the immune system to remain in balance. However, a few cells will stick around and form memory cells. These cells allow for a quick immune response if the same antigen is ever encountered again.

Vaccines take advantage of this system by presenting the immune system with a weakened form of a virus. Macrophages are able to eat up the weakened virus and present it to B and T cells, which both become activated. These cells are quickly able to suppress the virus and then, as the immune system is shutting down, form memory cells, which can respond to real invaders if they ever enter the body.[4]

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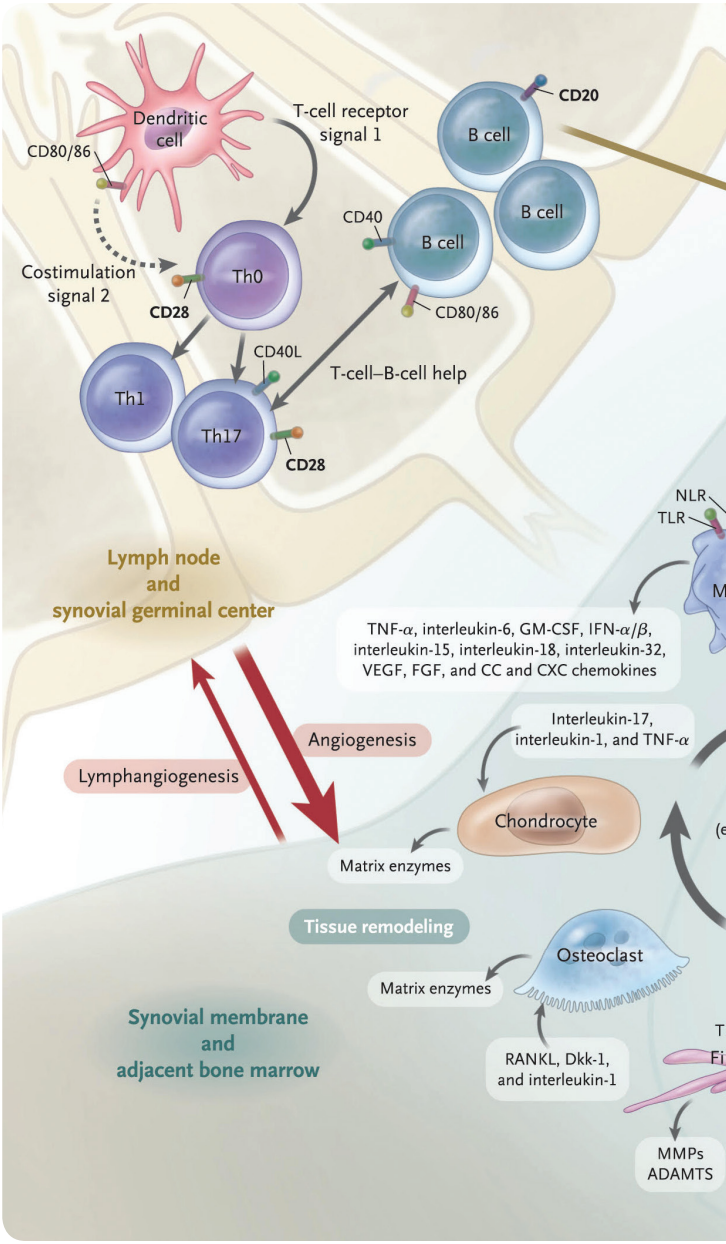
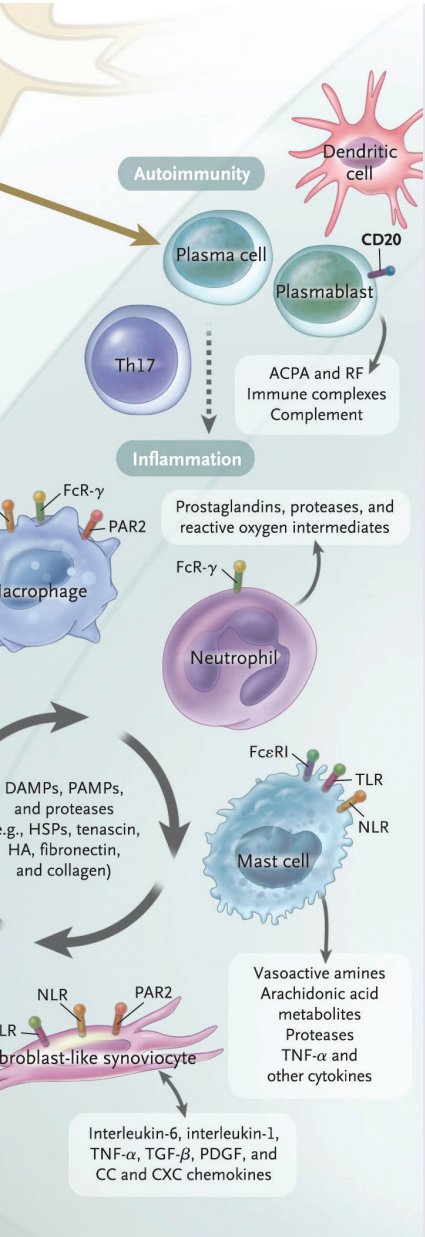

Dendritic cell
CD80/86
T-cell receptor signal 1
CD20
B cell
B cell
CD40
B cell
CD80/86
Costimulation signal 2
CD28
Th0
CD40L
T-cell–B-cell help
Th1
Th17
CD28
NLR
TLR
Lymph node and synovial germinal center
TNF-α, interleukin-6, GM-CSF, IFN-α/β, interleukin-15, interleukin-18, interleukin-32, VEGF, FGF, and CC and CXC chemokines
Angiogenesis
Lymphangiogenesis
Interleukin-17, interleukin-1, and TNF-α
Chondrocyte
Matrix enzymes
Tissue remodeling
Osteoclast
Matrix enzymes
Synovial membrane and adjacent bone marrow
RANKL, Dkk-1, and interleukin-1
MMPs
ADAMTS



Adaptive and Innate Immune Processes within the Joint in Rheumatoid Arthritis

The costimulation-dependent interactions among dendritic cells, T cells, and B cells are shown as occurring primarily in the lymph node; these events generate an autoimmune response to citrulline-containing self-proteins. In the synovial membrane and adjacent bone marrow, adaptive and innate immune pathways integrate to promote tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of rheumatoid arthritis.

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What is wrong with my immune system?

Autoimmune and inflammatory disorders, which account for the majority of rheumatic diseases, occur when an individual's body mistakenly attacks itself. Why this happens is currently unknown. Normally, it is the responsibility of the innate immune system to tell foreign invaders apart from a person's own body. To accomplish this, immune cells that react strongly with self-antigens (antigens that originate within the body and to which an individual is typically tolerant) are either killed or suppressed during their development. Normally, this process is very effective, with up to 98% of T-cell precursors that react to self-antigens dying before they get the chance to mature.[1]

T cells undergo both a positive and negative screening process during their development. First, they

undergo positive screening in the thymus to make sure that they are able to react with either a class I or II major histocompatibility complex (MHC) molecule (see **"What is a T cell?"** section for more information on MHCs), which is key to their ability to function during an immune response. Cells that pass this test then move on to negative selection. This process presents T cells with a self-antigen located on the surface of an antigen presenting cell (APC). Any T cell that binds too tightly to this complex is killed, while all other T cells are allowed to complete the maturation process. A similar process occurs in the bone marrow for B cells, with any B cell being destroyed before it matures if it expresses an antibody that strongly interacts with a self-antigen.[1]

When this process fails, autoantibodies form. This allows an immune response to occur against a person's own body, resulting in damage to any part of the body that expresses that antigen.

Occasionally, as the body is fighting off an infection, the antibody-antigen complex that forms can collect in the bloodstream and deposit in blood vessels. This leads to the development of chronic inflammatory disease. In other instances, if a foreign antigen closely resembles a self-antigen, the immune system can confuse the two antigens and end up attacking normal tissue by accident.[1]

Why some people develop a problem with their immune system is unclear. What is currently known is that women are twice as likely to develop an autoimmune disorder as men.[2] Some autoimmune disorders, such as lupus, affect African-Americans and Hispanics in greater

numbers than Caucasians, while others appear to have a genetic component. Environmental factors, including diet and smoking, also likely play a key role since many disorders have a higher incidence in Western societies.[3]

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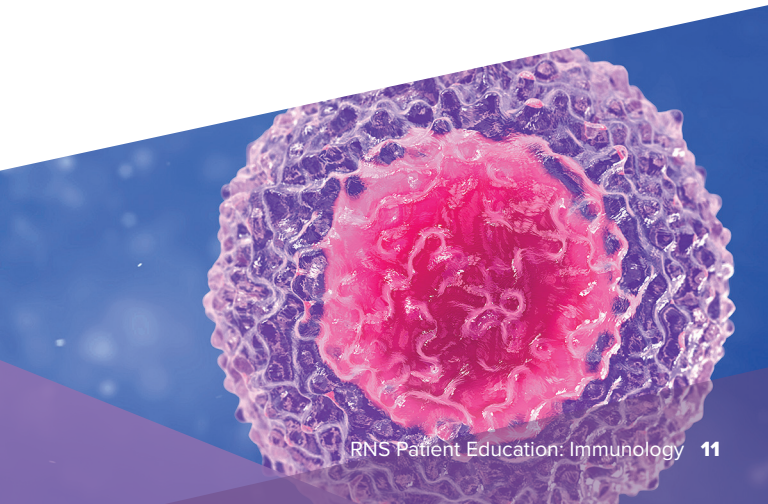
What is a T cell?

A T cell is a type of lymphocyte that develops from stem cells in the bone marrow and matures in the thymus.[1] T cells are part of the **adaptive immune system** and are capable of delivering a diverse set of immune responses referred to as cell-mediated immune reactions.

There are two main classes of T cells—cytotoxic T cells and helper T cells—that produce an antigen-specific immune response. They are only able to function over a short range, either staying in the lymphoid tissue or migrating to the site of infection. Their role in the immune response is more complicated than their B cell counterparts.

The two types of T cells function in very different ways. Helper T cells, also referred to as CD4+ T cells, help to activate B cells, other T cells, and phagocytes by producing and releasing a number



of different chemical mediators. When an antibody attaches to a foreign invader, the cytotoxic T cell—also called a CD8+ T cell—becomes activated against the infected cell and kills it.[2]

T cells are activated to proliferate and differentiate when they encounter a piece of the antigen attached to a major histocompatibility complex (MHC) molecule on the surface of an antigen presenting cell (APC), which they come across in the lymphoid tissue (ie, lymph nodes, spleen).

There are two types of MHC molecules—MHC I and MHC II.

MHC I molecules are found on all healthy nucleated cells in the body. When a healthy cell's cytoplasm is invaded by a foreign antigen, the cell breaks it up and displays a small piece of the antigen on the MHC I molecule on its surface. Antigens that are displayed on MHC I molecules are mainly recognized by cytotoxic T cells.

MHC II molecules are only found on specialized cells, such as dendritic cells, macrophages, and B cells. These cells display antigens from microbes that enter a cell's vesicles. Antigens that are displayed on MHC II molecules attract mostly helper T cells. The ability for MHC molecules to present antigens from microbes that are inside cells allows T cells to recognize and eliminate microbes that are already inside of a cell.[2]

While many autoimmune disorders are considered to be B-cell driven, T cells are known to play a crucial role in the development of a number of rheumatoid disorders by enhancing the develop-

ment of autoantibodies produced by B cells.[3,4] T cells may not be directly responsible for making the autoantibodies that attack the body, but the immune system could not function without their help.

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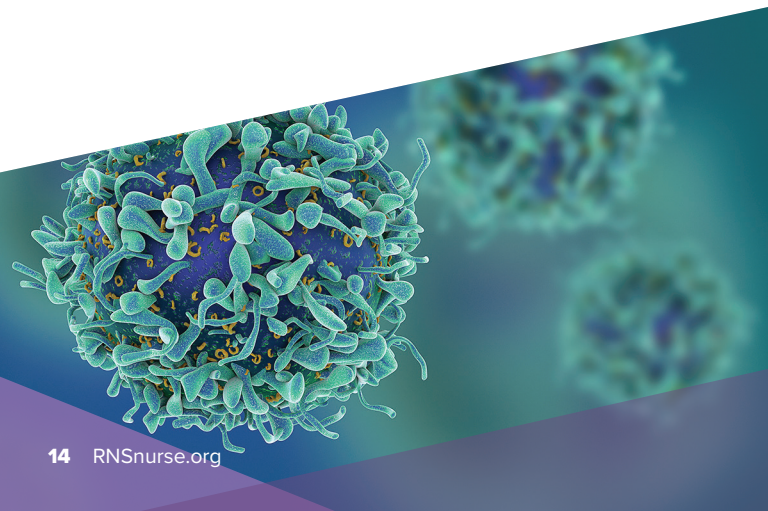
What is a B cell?

A B cell is a type of lymphocyte that develops from stem cells in the bone marrow and is responsible for making antibodies that fight foreign invaders.[1] B cells make up the humoral immunity aspect of the immune system, which is particularly good at fighting extracellular invaders. Each B cell is capable of producing only one specific antibody, and each has a unique antigen-binding site.

As B cells circulate throughout the body, they are on the lookout for foreign antigens—such as bacteria, viruses, or toxins—which can be freely circulating or attached to the surface of a microbe. This is a key difference between B and T cells; T cells recognize invaders *inside* cells, while B cells recognize invaders *outside* of cells.

When a naive B cell encounters an antigen that is complementary to its antibody receptor, it



becomes activated with the assistance of helper T cells. It clones itself and changes into an antibody-secreting effector cell, also called a plasma cell, which can produce large amounts of the necessary antibody.[2] The antibodies then help to neutralize the foreign invader and mark it for destruction by other immune cells, although the antibodies don't actually kill the invader themselves.

Once the invader is destroyed, memory cells are formed, which allows the immune system to respond faster and more efficiently when they encounter the invader again.[2]

B cells play a prominent role in a number of rheumatic conditions. They are responsible for producing the autoantibodies that are present in many disorders, including rheumatoid factor, anti-DNA antibodies, and more.[3,4] They also play roles in antigen presentation to other immune cells as well as cytokine secretion, which promotes the inflammation present in rheumatic disorders.

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Cell Types Involved in Rheumatic Diseases

Cell Type	Description
B cell	• Specialized white blood cell central to the humoral immune response and adaptive immune system • Produces antibodies against soluble antigens
Dendritic cell	• A type of antigen-presenting cell that captures, processes, and presents antigens to T cells • Also presents appropriate costimulation molecules to induce a T cell response
Fibroblast	• Connective tissue cell that produces and maintains the extracellular matrix
Monocyte	• Type of white blood cell typically involved in infection response • Differentiates into macrophages in the presence of damaged tissue
Macrophage	• A specialized monocyte that removes dead cell material via phagocytosis
Neutrophil	• Specialized cell of the innate immune system that ingests and destroys pathogens • Partly responsible for inflammatory tissue damage
Osteoblast	• Type of bone cell that creates new bone tissue
Osteoclast	• Type of bone cell that resorbs bone tissue • Implicated in joint damage in RA patients
T cell	• Specialized white blood cell central to the cell-mediated immune response • Helper T cells (CD4+ T cells) stimulate the secretion of proinflammatory cytokines (IL-1, IL-6, TNF-α), production of MMPs, and production of osteoclasts

IL-1 = interleukin-1; IL-6 = interleukin-6; MMP = matrix metalloproteinases; TNF = tumor necrosis factor

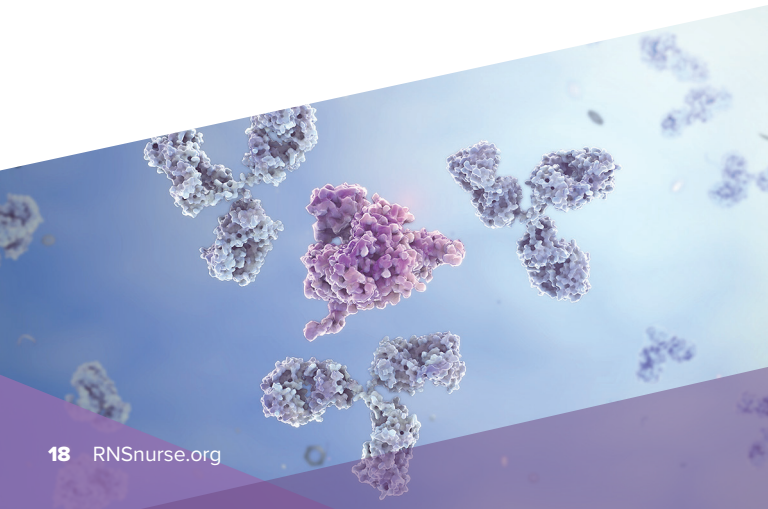
Think of it as...
The air traffic controller who takes in information and disseminates it to a number of different sources
The switchboard operator who fields incoming calls and relays the most urgent messages to the authorities
The flooring contractor who provides a strong foundation and subfloor
The superhero who gets ready to change shape in the face of danger
The trash collector who cleans up all types of debris
A steamroller that indiscriminately crushes everything in its path
The construction crew that builds new structures
The demolition crew that knocks down old structures
The firefighter who reacts immediately to any threat with broad, nonspecific life-saving skills

Reference:
Carter SC, Patty-Resk C, Ruffing V, Hicks D, eds. Core Curriculum for Rheumatology Nursing. First Ed. Rheumatology Nurses Society; 2015.

What is an antibody?

Antibodies are Y-shaped proteins that play a key role in stopping foreign invaders, referred to as antigens, in the body. When a foreign invader such as a bacteria, virus, or toxin enters the body, the immune system responds in a number of different ways. One way is through the formation of antibodies, which are made by B cells. Each antibody is made to specifically match one specific antigen that is encountered in the body. These antibodies are able to attach to the antigen and mark it as something that the body needs to destroy. T cells are then recruited to destroy the cells marked with an antibody. Once the invader has been destroyed and the immune response is shut down, the antibodies remain in the body, ready to attack if the invader is encountered again.[1,2]

There are a number of different types of antibodies produced by the immune system. These include immunoglobulin G (IgG), IgA, IgE, IgM, and



IgD antibodies. Each of these antibodies has a different role in protecting the body.[2]

- **IgG:** Neutralizes microbes and toxins and activates complement. IgG antibodies provide long-term immunity. IgG antibodies are able to cross the placenta and pass through the mother's milk to provide early immunity to newborns.
- **IgA:** Secreted by the respiratory and GI tract to neutralize microbes and toxins
- **IgE:** Defends against parasitic worms and plays a key role in allergic diseases
- **IgM:** Type of antibody secreted by naïve B lymphocytes. IgM is the first antibody to respond to an antigen.
- **IgD:** Antigen receptor for naïve B lymphocytes

Vaccines work to create disease immunity by imitating an infection and promoting the formation of specific antibodies. By giving the body a small sample of a virus or bacteria, the immune system is able to make memory T cells and antibodies that can be used later should the body encounter the disease.[3]

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What is a cytokine?

Cytokines are molecules that cells use to communicate with one another. Their primary role is to help promote the body's immune response by stimulating the movement of cells toward the site of infection, inflammation, or trauma. During times of infection or inflammation, cytokines can increase by a thousand-fold to help promote an immune response.[1] Examples of cytokines include interferon and interleukins.

Nearly all cells are capable of expressing some cytokines, such as interleukin-1 (IL-1), IL-6, and TNF-α, especially endothelial cells, epithelial cells, and macrophages. These cytokines can bind to cytokine receptors on many different types of cell membranes. Most cytokine receptors signal cells using one of the Janus kinase (JAK) family of molecules, which activate signal transducers and activators of transcription (STAT) proteins.[2] TNF-α and other cytokines are also capable of increasing the expression of RANKL, which plays an important role in the development of rheumatoid arthritis.[3]

Cytokines play an important role in many autoimmune disorders, particularly those seen in rheumatology. Activated B and T cells, plasma cells, mast cells, and activated macrophages all contribute to autoimmune disorders and are recruited and activated by cytokines. A number of cytokines have

been found to contribute to the activation of these cells in rheumatic disorders, including IL-1, IL-2, IL-6, IL-8, IL-17, IL-23, and TNF-α.[1] Because of the prominent role that cytokines play in rheumatic disease, many therapies that are used to treat these disorders are designed to inhibit cytokines and prevent them from recruiting and activating immune system cells.[3,4] These include TNF-α inhibitors, JAK inhibitors, and glucocorticoids, among others.

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Cytokines and Other Molecules Involved in Rheumatic Diseases

Proinflammatory cytokines	Description
IL-1	• Stimulates the release of MMP from fibroblasts and chondrocytes
IL-6	• Activates T cells, induces the acute-phase response, and stimulates the proliferation of synovial fibroblasts • Produced by T cells, monocytes, macrophages, and synovial fibroblasts
TNF	• Promotes the initiation and progression of inflammation • Produced primarily by monocytes and macrophages, but also by B cells, T cells, and fibroblasts
Anti-inflammatory cytokines	**Description**
IL-4	• Inhibits the production of IL-1, IL-6, IL-8, and TNF • Decreases inflammation and inhibits cartilage damage
IL-10	• Inhibits the production of IL-1 and TNF • Reverses cartilage degradation
Other molecules	**Description**
CTLA4	• An antigen found on the surface of T cells • T-cell activation requires a "costimulatory" signal, which occurs when the T-cell receptor (TCR) binds with another surface antigen, CD28
JAK	• A family of intracellular enzymes that process cytokine signals through the JAK-STAT signaling pathway
MMP	• A family of enzymes capable of degrading extracellular matrix proteins • Implicated in synovial inflammation
RANKL	• Promotes osteoclast differentiation and joint cartilage invasion

CTLA4 = cytotoxic T-lymphocyte antigen 4; JAK = Janus kinase; IL-1 = interleukin-1; IL-4 = interleukin-4; IL-6 = interleukin-6; IL-10 = interleukin-10; MMP = matrix metalloproteinases; RANKL = receptor activator of nuclear factor kappa-B ligand; TNF = tumor necrosis factor

Think of it as...
Music that can be felt through the floor
Music played over the loudspeaker
The DJ who plays his own music and regulates the timing, speed, and flow of music played by others
Think of it as...
Soothing music that relays calming signals
A mute button that inhibits the music of pro-inflammatory cytokines
Think of it as...
The ignition on the fire truck, without which firefighters cannot respond to threats
A cable car that provides the only access down highly desirable roads
Termites that can degrade the subfloor
The chief of the demolition crew who directs the wrecking ball toward particular structures

Reference:
Carter SC, Patty-Resk C, Ruffing V, Hicks D, eds. Core Curriculum for Rheumatology Nursing. First Ed. Rheumatology Nurses Society; 2015.

How do medications help treat my rheumatic disorder?

Since the underlying problem in many rheumatic disorders is inflammation or an autoimmune process, most treatments are designed to decrease or suppress the body's immune system. Many treatments, such as glucocorticoids and nonbiologic disease modifying anti-rheumatic drugs (DMARDs), affect the entire immune system. Meanwhile, biologics, including TNF-α and Janus kinase (JAK) inhibitors, aim to target a more specific component of the immune system.

It is important to recognize that none of our current treatments are designed to be curative in nature. The goal with the development of biologic therapies is to weaken the specific part of the immune system that is responsible for an

individual's disease while limiting the adverse effects associated with broad inhibition of the immune system.[1]

Whether the entire or a small part of the immune system is inhibited, the overall immune-mediated response is generally reduced. While this may help to improve an individual's original symptoms, an unfortunate consequence is that this inhibited response also suppresses the immune system when a person needs it to work, such as exposure to the flu or a cold virus.[2] Patients taking nonbiologic DMARDs, glucocorticoids, biologics, and small molecule JAK inhibitors should be counseled about signs of infection and given information advising them to call their clinician's office should they develop certain types of illnesses.

Patients being treated with nonbiologic or biologic therapies should also be encouraged to stay up-to-date with their vaccinations. In general, patients with a rheumatic disease should receive the following vaccinations:[3]

- Annual influenza vaccine using the killed variation
- Herpes zoster vaccine (live attenuated) in all patients >50 years of age prior to starting therapy with a biologic therapy or tofacitinib
- Pneumococcal vaccine 5 years after the diagnosis of chronic disease, plus a one-time revaccination at age 65 years if the first vaccine was given before 65 years of age

- Hepatitis B vaccine, per Centers for Disease Control and Prevention (CDC) recommendations
- Human papillomavirus per CDC recommendations

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Is there anything that I can do to fix my immune system?

The immune system is complex, involving many different components, thereby making it very difficult to "fix." However, there are steps that a patient can take to optimize their immune system and bring it back into overall balance. This primarily involves a healthy, well-balanced lifestyle. While none of the following steps will cure an autoimmune disorder, taken collectively, they can improve patients' overall health, reduce the chances of developing an infection, and improve how they feel.

Specific recommendations include:[1-3]

- No smoking
- Regular exercise
- Maintaining a healthy weight

- Limiting the amount of alcohol consumed
- Getting adequate sleep (>6 hours a night)
- Minimizing stress
- Avoiding infection by regularly washing hands and not eating undercooked meats
- Eating a well-rounded diet high in fruits and vegetables

A number of claims can be found online offering advice to patients with rheumatic diseases about ways to return balance to or boost an immune system, promising a "cure" with the appropriate lifestyle modifications. While these snake oil promises sound exciting, there is currently no known cure for autoimmune disorders, and the potential impact that many unstudied remedies can have on the body is unknown. Herbal remedies and supplement claims that extend beyond their studied role in nutrition are not regulated.[4] For this reason, the American College of Rheumatology (ACR) recommends against the use of most of these products.

Comprehensive information regarding complementary and alternative therapy can be found on the National Center for Complementary and Integrative Health website (https://nccih.nih.gov/).

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